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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/078,278	02/20/2002	Robert E. Wagner JR.	007274-01	3427

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EXAMINER	
BAUSCH, SARAE L	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/078,278	WAGNER ET AL.	
	Examiner	Art Unit	
	Sarae Bausch	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is written in response to applicant's correspondence submitted on 05/01/2006.

2. Currently, claims 56-75 are pending in the instant application. Claims 1-55 have been canceled. Claim 56 has been amended. This action is written in response to applicant's correspondence submitted 05/01/2006. All the amendments and arguments have been thoroughly reviewed but were found insufficient to place the instantly examined claims in condition for allowance. The following rejections are either newly presented, as necessitated by amendment, or are reiterated from the previous office action. Any rejections not reiterated in this action have been withdrawn as necessitated by applicant's amendments to the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is Final.**

Claim Status

3. It is noted that claim 56 does not comply with 37 CFR 1.121. Applicant is reminded that the removal of the text in a claim should be crossed out or bracketed and new text should be underlined to indicate which text is being removed and which text is being added. In the instant case, claim 56 recited "without the removal of unreacted probes" in the last line of the claim and applicants amended the claim and removed the phrase and added new language. However, the previous phrase "without the removal of unreacted probes" was neither cross out or put into brackets to indicate the removal of the phrase.

Withdrawn Rejection

4. The rejections of claims 56-69, under 35 U.S.C. 112, second paragraph, made in section 6, of the previous office action mailed 11/30/2005, is withdrawn in view of the amendment to the claims.

Declaration

5. The declaration under 37 CFR 1.132 filed on 05/01/2006 is acknowledged and is insufficient to overcome the rejection under 103(a) of claims 56-75. The declaration is addressed in section 11 below.

Maintained Rejection

Claim Rejections - 35 USC § 112- New Matter

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 56-75 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was previously presented in section 4 of the previous office action mailed 11/30/2005 and has been rewritten to accommodate the amendment to claim 56.

Newly added claim 56 with the recitation "wherein a positive signal is generated only when two or more components are co-localized, thus allowing detection" is not supported in the specification and raises the issue of new matter. The specification teaches detecting the presence

of immobilized probe DNA or RecA bound to MutS wherein the presence of the bound probe or RecA is indicative of the presence of the mutation or SNP in the test DNA (see page 6, lines 22-25) but does not mention a positive signal is generated only when two or more components are co-localized. The specification teaches the if the test DNA sequence is identical to the probe then the test is negative (see page 7, lines 15-17), however the specification does not teach generating a positive signal. Furthermore the specification teaches the most successful assay formats on page 22, lines 22-30 but does not teach that a positive signal is generated *only* when from two *or more* components are co-localized. As discussed in MPEP 2163.05, section II, the introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph.

Response to Arguments

8. The response asserts on page 7 of the response mailed 05/01/2006 that the amendment to removed the recitation of "without removal of unreacted probes" and assert that the specification on page 19, lines 3-10 and on page 21, line 17 support the recited language. This response has been thoroughly reviewed but not found persuasive. The specification teaches that the number of positive signals in a sample is an indication of the genotype (see page 21, line 18), the flow cytometer is set to detect a signal of both labels on MutS and RecA and/or probe (see page 19, lines 3-7); however the specification does not teach co-localization of two "or more" components nor teach that a positive signal is generated "only" when two or more components are co-localized.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 56-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kigawa et al (US Patent 5965361 Oct 1999) in view of Nolan et al. (WO 99/22029 May 1999).

Kigawa et al. teach a method for detecting the presence of a double stranded target nucleic acid sequence using a probe/RecA complex (abstract). Kigawa et al. teach the use of a nucleic acid probe, typically a single stranded nucleic acid prepared by a virus, plasmid, or a cosmid, a probe DNA moiety excised from a vector, or probe from an oligonucleotide synthesizing method (instant claim 58) (see column 5, lines 64-67 and column 6, lines 1-10). Kigawa et al. teach probes with 90-95% homology to the target nucleic acid sequence and a length of 100 to 1500 bases but longer or short polynucleotide probe may be used (instant claim 59) (see column 6, lines 12-18). Further, Kigawa et al. teach nucleotide probes with a label, such as a fluorescent indicator, a radioactive label or a ligand that can be bound to a specific reporter molecule such as biotin and digoxigenin (instant claim 60) (see column 6, lines 23-28). Kigawa et al. teach the use of RecA protein with a detectable label or ligand, such as a fluorescent indicator, a chemiluminscent agent, an enzymatic label, a radioactive label, biotin or digoxigenin (instant claim 61-62, 65 and 66) (see column 6, lines 61-67). Kigawa et al. teach alternatively detecting the double-stranded target nucleic acid by allowing the probe/RecA complex to react with an anti-RecA antibody with or without a label or ligand (instant claim 64 and 66) (see column 10, lines 50-58). Kigawa et al. teach the hybridization reaction can be performed in the

presence of another protein, such as a single-stranded binding protein, if necessary to accelerate the reaction (instant claim 44) (see column 9, lines 18-22). Kigawa et al. teach detecting the presence of the double stranded target sequence by detecting a fluorescent signal derived from the RecA protein having a fluorescent label included in the probe/RecA complex bound to the target sequence detected with a fluorescent microscope or flow cytometer (instant claim 68-69 and 70) (see column 10, lines 24-32). Kigawa et al. teach the use of the probe/RecA hybridization method to detect various types of chromosomal aberration such as deletion and insertion (see column 13, lines 18-21). Kigawa et al. does not teach the use of MutS protein with RecA for the detection of chromosomal aberrations.

Nolan et al. teach a method of detection of DNA polymorphisms including nucleotide polymorphisms, insertions, and deletions (page 1, line 6-7) that includes using an immobilized mismatch-binding protein-coated microspheres to bind fluorescently labeled, mismatch-containing DNA by flow cytometry (instant claims 68-69) (page 4, lines 24-26). Nolan et al. teach genomic DNA amplified by PCR using fluorescently labeled nucleotide triphosphates (instant claim 57-58 and 71) (page 4, lines 26-28). Nolan et al. teach microspheres bearing immobilized mismatch-binding protein and further teach mismatch binding proteins to include bacterial mismatch-binding protein, MutS, or any other protein that recognizes DNA base pair mismatches which can be immobilized on microspheres by physical absorption or by the use of an affinity tag which binds to an affinity partner immobilized on microspheres, such as biotin affinity tag and avidin/streptavidin binding partner (instant claim 60, 62-64, 73-75) (page 5, lines 23-29 and page 6 Table).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of detecting the double stranded target nucleic acid using a probe/RecA complex by Kigawa et al. to include the MutS protein detection system as taught by Nolan et al. to improve the method of probe/RecA detection system by Kigawa et al. The ordinary artisan would have been motivated to improve the method of detecting the double stranded target nucleic acid sequence using the probe/RecA hybridization system by Kigawa et al. with the mismatch binding protein, MutS immobilized to microspheres taught by Nolan et al. because Nolan et al. teaches that the MutS immobilized detection system provides a high throughput, small volume, and washless method for detecting SNPs in DNA (page 4, lines 5-6). Further, the method of Nolan et al. allows for rapid scanning of mismatch DNA which would improve the detection of RecA/probe complex formation taught by Kigawa et al. The ordinary artisan would have had a reasonable expectation of success that the use of MutS could be used in the method by Kigawa et al. because Nolan et al. teach that the use of MutS immobilized onto microspheres for the detection of SNPs with flow cytometry provides multiparameter detection with excellent sensitivity in a homogenous assay format and multicolor fluorescent detection can be exploited for the simultaneous detection of dozens, or potentially hundred of analytes in a single sample (page 3, lines 9-14).

Response to Arguments

12. The response asserts that MutS is known to have very specific requirements for mismatch binding in duplex DNA and there was no reasonable expectation of success with triplex and quadreplex structures. This response has been thoroughly reviewed but not found persuasive. Even in light of the references and declaration filed by applicant, at the time the invention was

filed, it was known in the art that MutS can bind triplex structures. Contrary to applicants arguments, one of ordinary skill in the art would have had a reasonable expectation of success because in fact well known in the art at the time the invention was made, it was known that MutS binds triple helix structures. For instance, the ability of immobilized mismatch binding proteins, including MutS, to bind to and detect triple helix DNA is specifically disclosed by the prior art of Wagner et al. (US Patent 6120992, Sept. 19, 2000) (see column 22, lines 52-60). Therefore, based on the teachings in the art, there was a reasonable expectation of success that MutS would bind a triplex structure.

With regard to the declaration filed under 37 CFR 1.132, it is acknowledged that the ability of MutS to bind mismatches is complex and the binding of MutS will be dependent on the nature of the mismatch, state of the mismatch, and the surrounding nucleotide as taught by Dohert et al, Su et al, Fazakerley et and Jones et al. However, as discussed above, even though MutS has different affinities for different mismatches, as taught by Dohert et al. and Su et al., it was known at the time the invention was filed that MutS does bind triplex complexes. Furthermore, even though "looped out" configurations are not seen by MutS as taught by Fazakerly et al, a triplex is not a "looped out" configuration, a triplex forms a duplex formation and therefore it is not unexpected that MutS would bind this configuration. With regard to the teaching of Jones et al., Jones et al. teaches that the ease of recognition of mismatches will depend on the surrounding base composition, however Jones et al. does not teach that MutS will not recognize a complex based on the surrounding base composition nor that MutS will not bind a triplex formation, Jones, as well as Dohert and Su teach that the affinity of MutS will vary depending on the environment but this does not support Applicants view that there is no

reasonable expectation of success that MutS will not recognize or bind a triplex, as Wagner et al. teach that MutS does bind triplex formation.

Furthermore, as stated in the previous office action, the instant specification teaches the mismatch repair system of E. coli recognizes mismatches in the hybrid overlaps, which states that prior to the invention it was known that the mismatch system binds hybrid structures (which includes two, three and four stranded structures) (see page 2, lines 25-30). Furthermore, the specification asserts that MutS binds to the duplex portion of the triple strand or D-loop structure (see page 8, lines 25-26). Although the claim recites contacting the DNA structure (three or four stranded structure) with MutS protein the claim is not limited to MutS detecting the mismatch in the three or four stranded portion of the DNA structure, as defined in the specification MutS binds the duplex portion of the three or four stranded portion of the DNA structure. Therefore, one of ordinary skill in the art would have been motivated to use MutS with RecA system as taught by Kigawa to allow for rapid scanning of mismatch DNA. Furthermore, one of ordinary skill in the art would have been motivated to use MutS with RecA for detection of mismatches because both MutS and RecA are part of the mismatch repair system of E. coli.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

13. No claims are allowable.

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912. The examiner can normally be reached on M-F 10am-7pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application

or proceeding should be directed to (571) 272-0547.

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Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER

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Art Unit 1634
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